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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GOLDBERG, JEANINE ANNE	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 12/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/979,513	DANIEL ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 9-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 9-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed October 3, 2004. Currently, claims 1-6, 9-13 are pending.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.

3. Any objections and rejections not reiterated below are hereby withdrawn.

Maintained Rejections

Priority

4. This application claims priority to foreign application Germany 199 22 052.2, filed May 14, 1999.

Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a translation of the foreign application should be submitted under 37 CFR 1.55 in reply to this action.

Drawings

5. The drawings are acceptable.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-6, 9-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Newly Amended Claims 3-6, 9-10, 12-13 are indefinite because it is unclear how all of the alternative or required steps are related. For example, it is unclear whether the expression profiles are determined in apoptosis regulating or cell growth regulating genes or mutated gene sequences or whether expression is determined for apoptosis regulating or cell growth regulating genes and mutation in genes are determined for analysis. Claim 1 has been amended to require detection of expression profiles, however, Claim 3 appears to allow for detection of differences. It is unclear whether this is a further analysis in addition to the expression profiles or whether this language was not amended in scope with Claim 1. It is unclear how Claim 3 and Claim 1 relate. Moreover, Claim 3 does not appear to contain any particular positive recitation of a method step. The claim contains a wherein clause, but this is not a positive active method step to further limit Claim 1. Further, the claim does not clearly provide what the steps of the method require.

B) Regarding claims 5, 6, the phrase "preferably" and "for example" renders the claims indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Response to Arguments

The response traverses the rejection. The response asserts the claims have been amended to render the rejections moot. Claims 5 and 6 still contain the rejected

language of preferably and for example. Thus for the reasons above and those already of record, the rejection is maintained.

C) Claims 4-6 are indefinite because it is unclear how more agents are determined. The claims have been amended to require a method for selecting therapeutic agents for the treatment of malignant disease by determining the expression profiles of one or more cell cycle genes. The preamble of the method if for selecting therapeutic agents for treatment of malignant disease, however the claim fails to provide any methods steps for selecting therapeutic agents. It is unclear whether the method is for determining expression profiles or whether the claims are for selecting therapeutic agents.

D) Newly amended Claim 9, 12 depends from Claim 1 which is drawn to a method of detecting the effect of different chemotherapeutic agents and evaluating them. Claim 9, however appears to be drawn to a method of determining treatment of leukemic diseases or non-leukemic neoplasias by determining the p53 expression or mutations and where if mutations are found, subject will not received a treatment if there are p53 mutations. It is unclear whether Claim 9 is directed to a method of detecting the effects of chemotherapeutic agents or to a method of selecting/treating with a therapy. Also, it is unclear whether Claim 9 further limits Claim 1. It is unclear what the steps of Claim 9 include and how they relate to Claim 1. Claim 1 is directed to comparing expression profiles and does not require determination of any p53 mutations. There is no indication of Claim 9 and Claim 1 limit each other. Similarly, Claim 10 does not clearly provide limiting steps for Claim 1. The method of Claim 1 has been amended to

be directed to comprising expression profiles, however Claim 10 is directed to status of gene products, mutations to design individual treatments. Claim 10, does not appear to use expression profiles of Claim 1 and further limit the claim.

E) Newly added Claim 13 is directed to genes are p53 and/or Bax. For the claim directed to p53, this limitation does not further limit Claim 1. Further, with regard to Bax in the alternative, the claim is unclear because the claim does not require genes generally, but specifically requires p53. Thus, the gene can not be Bax alone. In the even that the combination of Bax and p53 is required, the claim may be amended to require an additional gene for the expression profiling comprising Bax. However, as written, it is unclear what is intended by the instant claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 1, 3-6, 9-10 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Mukhopadhyay et al. (US Pat. 5,958,892, September 28, 1999).

Mukhopadhyay et al. (herein referred to as Mukhopadhyay) teaches a method for detecting the effect of different chemotherapeutic agents in caner by determining expression levels of p53. 2-methoxyestradiol) increases wild-type p53 levels in a human non-small lung cancer cell line associated with accumulation of cyclin dependent kinase inhibitor p21 WAF1/CIP1. Mukhopadhyay teaches methods for identifying compounds that will increase expression of wild-type p53. The screening technique will prove useful in the general identification of any compound that will cause an increased p53 expression in cancer cells (col. 4, lines 15-20). In screening assays to identify pharmaceutical agents which increase p53 levels in cancer cells, it is proposed that compounds isolated from natural sources may be assayed as candidates for the presence of potentially useful pharmaceutical agents. Mukhopadhyay teaches test cells can be used from patients or cell lines. To identify candidate substances as being capable of increasing p53 levels, one would measure or determine the p53 level of a cell. One would then add the candidate substance to the cell and determine the p53 content in the presence of the candidate substance (col. 4, lines 55-60). Assays that employ nucleotide probes may be used to identify the presence/absence of an intact p53 gene or Southern blotting, Northern blotting or PCR techniques (col. 6, lines 45-60). Mukhopadhyay teaches that Southern and Northern blotting techniques can be used to detect nucleic acid, including mRNA (col. 9, clines 35-40).

8. Claims 1-6, 9-10 are rejected under 35 U.S.C. 102(e) as being anticipated by Tocque et al. (US Pat. 6,509,153, January 2003).

It is noted that Applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

It is unclear from the instant claims how Claim 9-10 further limit the invention. For the reasons of the 112/2nd provided above, the claims have been broadly interpreted.

Tocque et al. (herein referred to as Tocque) teaches a method for determining the potential toxicity of test compounds. Tocque teaches that the invention is based specifically on genomics and on the development of genetic markers of toxicity that can be used to predict the toxic potential of any type of compound on any type of cell (col. 2). Genetic markers induced in a cell in a situation where cell signaling pathways are deregulated, particularly a cell in which cell viability and/or proliferation are deregulated (for example, in a situation of apoptosis), can be efficiently used to characterize the toxicity profile of test compounds. Methods for analysis of the potential toxicity of a test compound, comprising at least one hybridization step between a sample of nucleic acids from cells treated with this compound and a preparation of nucleic acids corresponding to genetic events, characteristic of situations of deregulation, the hybridization profile indicating the toxic potential of the test compound (col. 2, lines 55-62). Tocque teaches that a specific example of cells consists of tumor cells obtained from tumor biopsies, in which case the genetic markers according to the invention are

those characteristic of the tumor cell relative to a specimen of control tissue, particularly healthy tissue obtained by biopsy (col. 7, lines 15-20). Tocque teaches that the cells treated or not treated with the test compound can be of different origin and type. They are preferably mammalian cells, preferably humans cells from primary cultures or cell lines (col. 15, lines 25-30)(limitations of Claim 5). The cells can also be extracted from organs or tissues of animals treated or not treated with the compound (col. 15, lines 30-35)(limitations of Claim 5). Comparison of RNA expression in the untreated cell situation with that of situations treated with different products at different concentrations and treated times can be easily done by comparing the hybridization profiles of each probe from each situation under study (col. 16, lines 15-20). Tocque teaches that nucleic acid arrays may be used on solid support such as membranes, glass plates or bio-chips. MRNA probes from the healthy or pathological samples are then used in hybridization to identify messengers that are overexpressed or under expressed (col. 9). Tocque teaches the nucleic acid banks can be analyzed for expression of p53 (col. 14, lines 50-60). Figure 1 illustrates an array of nucleic acids and expression levels for untreated, ethanol-treated or cyclosporine-treated cells. Figure 2 illustrates the toxicity index for a variety of compounds assayed for. The hybridization profiles are analyzed by measuring the radioactivity with an InstantImager. Quantification of the individual hybridization intensities allows calculation of an index (Figure 2). This result shows that it is possible to classify different products according to their ability to induce the expression of makers that are differentially spliced during p-53 induced toxicity (col. 19, lines 60-70). Tocque claims a method of determining the toxic potential in a human cell

of a test compound by separately contacting, under conditions to allow hybridization, labeled nucleic acid probes to mRNA from untreated human cells and a library of immobilized nucleic acids comprising p53 and labeled nucleic acid probes to mRNA from human tells treated with a candidate therapeutic molecule and analyzing the hybridization profile to indicate the toxic potential of the candidate therapeutic molecule (col. 24, lines 35-55). Tocque teaches that expression of all or part of anti-oncogenes, promoters, initiators and mediators of apoptosis may be analyzed including RB, myc or any other protein fragment capable of interfering with cell grown and viability (col. 7)(limitations of Claim 2). Moreover, bcl2 family and caspases are taught (col. 10). Among the list of compounds analyzed includes aspirin, paracetamol, cyclosporine, clonidine, PMA, 5 FU, AXT, actinomycin D, for example (col. 19, lines 10-30)(limitations of Claim 6).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Spengler (US Pat. 5,876,972, March 1999).

It is noted that while the Claim depends from Claim 1, the claim does not appear to further limit Claim 1.

Spengler et al. (herein referred to as Spengler) teaches that cells lacking wild-type p53 are resistant to agents including fluorouracil, duxrubicin, etoposide which are alkylating agents. Whereas cells expressing wild-type p53 are sensitive to them and undergo cell death by apoptosis. Spengler teaches that p53 mutations dramatically reduce the probability that patients with B cell chronic lympocyte leukemia will enter remission after chemotherapy (col. 13, lines 60-65). Spengler teaches that the evaluation of the status of nucleic acids could serve as an decisive parameter for the extent and necessity of surgical resection and the need for adjuvant therapy.

Spengler does not specifically teach a method of treatment of CLL however, Spengler specifically teaches that cells expression wild-type p53 are sensitive to alkylating agents and allows cell death. However, cells that lack wild-type p53 are resistant to alkylating agents. Therefore, it would have been prima facie obvious to one of ordinary skill at the time the invention was made to have avoided administration of

alkylating agents to individuals who were resistant to the agents. The ordinary artisan would not have been motivated to have administered a agent which was predictively not going to be effective for inducing apoptosis to a patient. Therefore, the ordinary artisan would have been motivated to have avoided administering an alkylating agent to an individual with mutant p53 and would have selected a different therapy.

Response to Arguments

The response traverses the rejection. The response asserts that Spengler has not taught all of the limitations of Claim 9, however fails to provide any reasoning or rationale (page 9 of response filed October 3, 2004). For the reasons presented above, and in the 112/2nd rejection, Claim 9 is unclear how it relates to Claim 1. No clarification has been provided. Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

11. No claims allowable.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272- 0745.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J. Goldberg

Jeanine Goldberg
Patent Examiner
December 3, 2004